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Lymphoepithelial lesions of oral cavity- A proposed classification

Dental Science

KEYWORDS: Benign lymphoepithelial lesions, lymphoid tissue, Mikulicz's disease, sjogren's syndrome

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ABSTRACT

Among the tumours of the major and minor salivary glands there is a group that is characterized by the participation of two cellular components, the epithelium and the lymphoid tissue. Lymphatic tissues may be seen within or closely associated with oral mucosa in a variety of anatomic & pathologic conditions. Lymphoepithelial lesions are a group of lesions which share in common the dual participation of the epithelial tissue & the lymphoid tissue. The majority of these lesions involve the salivary gland & the neck region. In this paper the author has reviewed the main etiological and pathological features of these lesions and tried to classify the lesions in different groups according to their etiology, gross pathological and histological features and prognosis by reviewing different articles in literature.

INTRODUCTION

Lymphoepithelial lesions can be defined as a group of lesions which share in common the dual participation of the epithelial tissue & the lymphoid tissue. It constitutes a group of conditions almost exclusively discussed in connection with tumours and tumorous diseases of the parotid salivary gland and swellings of the lateral neck.[1] Lymphatic tissues may be seen either within or closely associated with oral mucosa in a variety of anatomic & pathologic situation. Primary lymph nodes are frequently seen in varying mucosal location. There may be localized collection of developing lymphocytes or lymphoid aggregation which apparently originate from undifferentiated connective tissue cell either idiopathologically or as a result of cell inflammation. Inclusion of epithelium within lymph node is a well documented phenomenon with the paraparotid & lateral cervical regions. Histologically, the lesions show an intimate association of epithelium & lymphatic tissue.

HISTORY

Benign lymphoepithelial lesion (BLEL) was first described in 1888, by German surgeon Johann Mikulicz in the report of a case. Patient has chronic, painless, bilateral enlargement of lacrimal gland followed by enlargement of submandibular & parotid gland. Inspite of the careful description of histopathology of this case, the term *Mikulicz's disease* was applied to a variety of cases of bilateral salivary or lacrimal gland enlargement, those caused by tuberculosis (TB), syphilis, sarcoidosis or lymphoma.[2] *Mikulicz's syndrome*, in contradistinction to the disease first described by Johann Mikulicz, represents an unrelated condition manifested by multiglandular lacrimal and salivary involvement secondary to diseases such as leukemia, tuberculosis, syphilis, sarcoidosis and lymphosarcoma. Shaffer and Jacobson were the first authors to separate Mikulicz's disease and Mikulicz's syndrome.[3]

In 1927, salivary gland enlargement was divided into two large categories:

a. Mikulicz's disease- if cause was unknown
b. Mikulicz's syndrome- if enlargement was associated with a known disease

Much has been written concerning possible systemic conditions giving rise to Mikulicz's disease, Sjogren's syndrome having been implicated both by Morgan and Hemenway.[4] In a presentation of four cases of Mikulicz's disease and six of Sjogren's syndrome, Hemenway pointed out that pathologic similarities between the salivary gland involvements in both the conditions exist. At the same time he demonstrated that no evidence supported the theory that Mikulicz's disease is a less highly developed form of Sjogren's syndrome.[4] The name benign lymphoepithelial lesion was proposed by Godwin in 1952.[5] One of the classifications of lymphoepithelial lesions was suggested by Bernier and Bhasker is given in Table 1 and the new proposed classifications are given in Table 2 and Table 3.

Table 1- Classification proposed by Bernier & Bhasker

1. Lesions arising from the salivary gland tissue included within the lymph nodes

a. Single or multiple cysts in the lymph node (benign lymphoepithelial cyst).
b. Papillary cystadenoma lymphomatosum.
c. Pleomorphic adenoma lymphomatosum.
d. Adenoma lymphomatosum.

2. Lesion primarily of lymphoid tissue but incidentally involving salivary gland

a. Mikulicz's disease (benign lymphoepithelial lesion or sialolymphadenitis).

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Table 2- New classification according to nature, gross morphology and histopathology

- Benign lymphoepithelial lesions.

1. Solid
a. Mikulicz disease (BLEL).
b Mikulicz syndrome (lymphoepithelial sialadenitis)
i. Tuberculosis.
ii. Cat scratch disase.
c. Sjogren's syndrome
d. Angiolymphoid hyperplasia with eosinophilia
2. Cystic
a. Salivary duct cyst.

2. Cystic
a. Salivary duct cyst.
b. Branchial cleft cyst.
c. Intraoral lymphoepithelial cyst.
d. Thyroglossal duct cyst.
e. Cyst associated with parotid.

4. Solid cystic
a. Warthin's tumor.
b. Salivary gland cyst as manifistation of HIV infection.

n **Malignant lymphoepithelial lesion**
a. Lymphoepithelial carcinoma.

Table-3- New classification according to whether the lesion is benign or malignant

- **Benign lymphoepithelial lesions.**

1. Mikulicz disease (BLEL).
2. Mikulicz syndrome (lymphoepithelial sialadenitis)
a. Tuberculosis.
b. Cat scratch disase.
3. Sjogren's syndrome.
4. Salivary duct cyst.
5. Branchial cleft cyst.
6. Intraoral lymphoepithelial cyst.
7. Thyroglossal duct cyst.
8. Cyst associated with parotid.
9. Angiolymphoid hyperplasia with eosinophilia
10. Warthin's tumor.
11. **Salivary gland cyst as manifistation of HIV infection.**

n **Malignant lymphoepithelial lesion**
1. Lymphoepithelial carcinoma.

MIKULICZ'S DISEASE (BLEL)

Pathogenesis: Mikulicz suggested that the disease was a result of an infectious or parasitic process penetrating the gland locally rather than hematogenously.[6] Morgan and Castleman considered it a primary lesion of the salivary gland duct system with secondary lymphocytic infiltration.[7] Bernier and Bhaskar suggested it be neither neoplasm nor a lesion in which epithelium plays an aggressive role; but primarily a lesion that incidentally involve the salivary gland.[8] Modern concept of immunologically mediated pathogenesis is now evolving. Mikulicz's disease is quite different from Sjogren's syndrome (SS) both clinically and histopathologically. Mikulicz's disease is suggested to be an IgG4-related systemic disease.[9]

Hisopathology:[2] There is focal infiltrate of small lymphocytes that causes replacement of glandular epithelium which leads to hyperplasia & metaplasia of ductal epithelium causing epi-myoepithelial islands. Lymphoid follicles with germinal center may or may not be present. Cells making up epi-myoepithelial islands not clearly identified. Previously it was considered that islands are formed by proliferation and squamous metaplasia of duct cells. More recently one study showed that these islands are composed of keratin containing epithelial cells & not cells with IHC characteristics of myoepithelial cells. Another study detected myoepithelial cells in EM but only in early stages. IHC study of BLELs & normal parotid gland carried out for cytokeratins & vimentin revealed two types of cells; one type contained cytokeratin [7,8,17,18], and 19 but no vimentin, similar to normal duct cells, whereas the other type contained same cytokeratin with vimentin, similar to profile of normal myoepithelial & ductal basal cells. Thus it was concluded that it is composed of mixed population of cells that have undergone metaplasia.

Diagnosis: It is by incisional or excisional biopsy. Histopathological diagnosis of BLEL should be followed by assessment of patient for presence of ocular or systemic components of SS. Cytology reveals rare epithelial cells among mixed population of lymphocytes & histiocytes but differentiation of BLEL from malignant lymphoma may not be possible.[10]

LYMPOEITHELIAL SIALADENITIS (LES)

It is a progressive autoimmune chronic inflammatory process, primarily of the parotid glands, in which dense infiltrates of T lymphocytes replace the acini and the residual ductal elements are stimulated to undergo hyperplasia, forming irregularly shaped islands of squamous epithelium. Whether gland enlargement is present or not, the tissue changes of LES are usually indicative of eventual development of SS.[11]

1. Tuberculosis:

TB lymphadenitis is most common extra thoracic form. Caused due to old age, malnutrition, and AIDS. There is asymptomatic enlargement of lymph node or salivary gland. Infection of salivary gland & cervical lymph node develops in two ways; first, focus of mycobacterial infection in tonsil, gingival sulcus or mucosal break liberates bacilli that ascend to gland via ducts or pass to lymph via lymphatic drainage; and second by hematogenous or lymphatic spread from lymph.

The swelling of glands occur which remain from weeks to years mainly in females between 23-35 years of age. Gland is usually painless and contains a cystic or solid nodule up to 5cm which is fixed and adherent to adjacent tissues, overlying skin is smooth & not erythematous.

Lymph node demonstrates multiple granulomas that are often confluent. Classic TB follicle is described as a focus of central necrosis surrounded by concentric bands of giant cells of langhan's and foreign body types, epithelioid cells, histiocytes & lymphocytes are also seen.

2. Cat-Scratch disease:

Transmission occurs by direct contact with healthy cat. Several erythematous papules mainly of upper extremities persist for 1-3 weeks & heal without scaring. Around 2 weeks after scratch, lymphadenopathies which are tender for first 1-2 weeks; mainly unilateral, involve single node or cluster of nodes. Histopahologically it is divided into 3 stages. Early stage is nonspecific with little distortion of nodal architecture, reactive follicular hyperplasia. Intermediate stage shows round or stellate granulomas of varying size, nodal architecture is distorted. In late stage there is central caseation & colliquative necrosis of granulomata are seen. Warthin-starry silver impregnation stain is used to demonstrate pleomorphic bacilli.

Most cases resolve spontaneously. This lesion is differentiated from other lesions by patient's history, serologic tests & cultures of lymph nodes.

SJOGREN'S SYNDROME (SS)

In Sjogren's syndrome there is immune-mediated destruction of exocrine glands. It should not to be confused with Mikulicz's disease (swelling due to nonspecific lymphocytic infiltrate accompanying non-connective tissue diseases such as hyperlipoproteinemia, malnutrition, diabetes, cirrhosis, tuberculosis, and sarcoidosis). There are two types of Sjogrens syndrome: Primary or sicca syndrome- isolated disorder of lacrimal and salivary glands; and Secondary or sicca complex- when associated with any other connective tissue diseases.

Histopathology- The microscopic features of SS are those of LES, the pathologic hallmark of SS is in the parotid gland. Although immunomarker studies have identified the presence of both B and T lymphocytes, the latter are the most abundant. With increasing numbers of infiltrating lymphocytes, progressive destruction and loss of acinar units take place. Once entire lobules have been infiltrated, it is not uncommon for germinal centers to form with a surrounding mantle of small lymphocytes resembling lymphoid hyperplasia in a node. These infiltrating cells do not cause lysis of the ductal elements; indeed, the ductal and periductal myoepithelial cells undergo hyperplasia, resulting in islands of epithelial cells that

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no longer contain well-defined ductal lumens. These epithelial foci are termed epimyoepithelial islands. The combination of acinar loss, lymphocytic infiltration, and epimyoepithelial islands constitute LES.[11]

LYMPHOEPITHELIAL (BRANCHIAL CLEFT) CYST

Histogenesis is controversial; the most widely accepted view of the pathogenesis is that the branchial cyst develops from incomplete obliteration of the branchial clefts with entrapment of epithelial remnants. Bhaskar and Bernier[2] postulated, however, that the neck cyst is not of branchial origin but that about 96% of them in reality represent cysts in cervical lymph nodes. The cystic change occurs in salivary gland epithelium which is trapped in the nodes of the neck during embryogenesis. Thus, they proposed that the lesion should be called 'lymphoepithelial cyst'. Many authorities still consider branchial cleft cysts and lymphoepithelial cysts as synonymous. While the issue is not completely resolved, lymphoepithelial cysts of lymph nodes or within the parotid gland as different entities from true developmental cysts arising from the branchial apparatus. Although the histology may be similar, the former type of cyst probably arises from salivary inclusions within lymphoid tissue.

Lymphoepithelial cyst of neck is mainly located anterior to sternocledomastoid muscle. It is seen in the all age group. Swelling is progressive or intermittent & pain may be a feature. Well circumscribed, asymptomatic masses in superficial portion the gland, which are firm or rubbery but may be compressible.

Histologically, epithelium lined multilocular cystic spaces enclosed by dense lymphoid tissue composed of small lymphocytes, plasma cells and germinal centers.

Differntial diagnosis includes: Low grade mucoepidermoid carcinoma, in which there is high proportion of mucin producing cell relative to squamous cells, presence of macro and microcyst; Acinic cell carcinoma, where there are intracystic papillary projections with a pseudoacinar pattern; multilayered epithelium with microcystic pattern, solid nodules of cells in the wall of cyst is seen; Warthin's tumor with squamous metaplasia, which has predominantly double layered granular, eosinophlic epithelium and papillary cystic pattern.

INTRAORAL LYMPHOEPITHELIAL CYST

There is cystic degeneration of epithelial inclusion in lymphoid aggregate in oral cavity. It is mainly seen in the floor of mouth and in the tongue between 15-65 years of age with male predominance. Cyst appears as a non-ulcerated freely movable mass, present from 1 month to a year. Patient may complain of swelling & discharge. Round to oval swelling of oral mucosa of normal color but when large they are yellow or white in color. Size of the lesion varies. Swelling is fairly mobile, superficial soft fluctuant, and sharply delineated.

It is believed that as oral cavity contains foci of lymphoid tissue, it is possible that ectopic glandular epithelium within these foci can undergo cystic change and form the lymphoepithelial cyst of oral cavity.[12]Some has view that intraoral lesions is a pseudocyst and that the epithelium could be of tonsillar crypt or salivary duct origin.[13]

It is usually lined by stratified squamous epithelium, devoid of rete ridges and may be keratinized. Occasionally, cyst may be lined by ciliated or non-ciliated pseudostratified columnar epithelium. Epithelium is closely enveloped by lymphoid tissue. In majority of cysts lymphoid tissue shows typical germinal centers. Lumen contains mainly desquamated parakeratotic cells and debris.

THYROGLOSSAL CYST[14]

During development, thyroglossal duct disintegrates by about 10th week, but cysts may form from residues of the duct at any point along its line of descent. The etiology of the cyst is not known but inflammatory conditions which lead to reactive hyperplasia of the lymphoid tissue adjacent to the remnants of the thyroglossal tract and may stimulate the epithelial remnants themselves have been mentioned, as has a blocked thyroglossal duct with an accumulation of secretion.

It is more common in women in their first three decades of life. The cysts are most commonly located in the midline of the neck in the area of the hyoid bone. Only about one quarter of lesions are found above the hyoid and only 2% are located in the mouth. Intra-oral lesions arise either in the floor of the mouth or at the foramen caecum. A proportion of thyroglossal duct cysts have an associated fistula. The cysts are usually in the midline and produce soft, movable, sometimes fluctuant, sometimes tender swellings. Occasionally, they may be located laterally. Classically, they lift when the patient swallows or protrudes the tongue. If they are located high in the tract they may cause dysphonia or dyspnoea.

Thyroglossal duct cysts are lined by a pseudostratified columnar epithelium which may be ciliated, or by stratified squamous epithelium. The latter type of epithelium is seen particularly in cysts close to the mouth. Thyroid tissue may be seen in the fibrous wall but is only found in up to 40% of lesions. Mucous cells may be present in the cyst lining and seromucous glands in the wall, particularly if the cysts are located in the lingual area. In the same region lymphoid tissue with prominent germinal centers may also be seen. Malignant change has occasionally been observed and it is reported that thyroid carcinoma may arise in approximately 1.5% of lesions. A review of the literature on the subject also revealed nine cases in which squamous cell carcinoma had developed.

It should be differentiated from the subhyoid bursal cyst & Sublingual dermoid cyst.

WARTHIN'S TUMOR[15]

Development-

1.Heterotopic salivary rest theory- Tumour arises from salivary gland tissue entrapped with paraparotid or intraparotid lymph nodes during embryogenesis. Another theory suggests that there is neoplastic transformation of parotid ductal epithelium & concomitant secondary proliferation of lymphoid tissue

2.Hypersensitivity theory- Allegra suggested that it is most likely delayed hypersensitivity response. The lymphocytes begin an immune reaction to the salivary ducts which undergoes oncocytic changes.

It occurs almost exclusively in parotid gland in lower portion. It is generally superficial and common in men in 6th decayed of life. Usual complaint is painless slow growing swelling over the angle of jaw. Involvement may be bilateral or multifocal. Usually 1-3cm in diameter, spherical in shape, well circumscribed with smooth surface & movable mass. Tumor feels doughy and compressible on palpation.

Cystic fluid may contain tiny, visible tissue fragments. Smear consists of lymphocytes and clumps of oncocytic epithelial cell. Atypical epithelial features are seen because of the oncocytes with irregular nuclei, clumped chromatin & loss of granular cytoplasm.

Grossly there is spherical or oval mass that is covered by a thin, tough capsule, which is usually intact. Tumor has smooth, red-gray, lobulated surface and the consistency varies from fluctuant to firm and rubbery. Cut surface shows multiple cysts.

Combination of lymphoid matrix and papillations of eosinophilic epithelial cells forming cystic spaces presents a distinct and pathognomic histopathologic picture. Epithelial cells arranged in two cell layers of uniform rows; columnar approximate the cystic space and inner cell layer which is cuboidal and polygonal is finely granular and distinctly eosinophilic.

It should be differentiated from papillary cystadenoma where there is sparse and unoraganized lymphocytic infiltrate, acinic cell carcinoma, muco-epidermoid carcinoma (low-grade) and sebacious lymphadenoma.

SEBACIOUS LYMPHADENOMA[15]

It is a rare benign tumor composed of well-circumscribed, variably shaped nest of sebaceous gland and duct within a background of lymphocytes and lymphoid follicles. There is minimal cytological atypia and no tendency to local invasion. Size varies between 1-6cm and is usually encapsulated. It may be present as solid, multicystic or unicystic masses that range in color from yellow to yellow-white.

Tumor is composed of variably sized sebaceous gland admixed with salivary ducts in a lymphoid background. Histiocytes and foreign body giant cell inflammatory reaction is commonly observed. There is presence of identifiable residual lymph node. Intracellular and intraductal mucin is rarely found.

SALIVARY GLAND CYST AS MANIFESTATION OF HIV INFECTION

Holliday *et al*[16] reported an association between lympho-epithelial cysts of the parotid, cervical lymphadenopathy and infection by HIV. Fine needle aspiration showed benign lymphocytes and squamous or cuboidal epithelial cells. Histologically, the lesions consisted of cysts lined by cuboidal and squamous epithelium surrounded by lymphoid tissue with prominent germinal centres. The authors warned that the CT findings of multiple parotid cysts and cervical adenopathy may indicate, before the onset of opportunistic infections, that the patient is infected with the HIV virus. The patients should be referred for HIV testing and parotidectomy should be deferred.

Histologically, HIV-associated lymphoepithelial cysts may be similar to cystic change in lymphoepithelial lesions of the type seen in Sjögren's syndrome. However, lesions in HIV patients are associated with diffuse infiltrative lymphocytosis syndrome (DILS) in which there is a CD8 lymphocytosis and infiltration of predominantly CD8 positive lymphocytes in the salivary glands.[17] In lymphoepithelial lesions, the lymphocytes are predominantly of the CD4 subset. Although HIV patients are at risk of lymphoma development, HIV-associated lymphoepithelial cysts are not regarded as pre-lymphomatous and do not appear to progress to MALT-type lymphomas as seen in Sjögren's syndrome related lesions. Another distinguishing feature is the presence of multinucleated giant cells in HIV-associated lesions. These have been shown to contain p24 (HIV-1) protein in immunocytochemical studies.[18]

LYMPHOEPITHELIAL CARCINOMA[19]

The term malignant lymphoepithelial lesion is confusing since it does not imply which cell type is malignant; therefore, the term lymphoepithelial carcinoma is used to clarify that the epithelial component rather than lymphoid element is malignant.

Although it constitutes only 0.4 percent of salivary gland neoplasms, there are unique and distinct geographic and ethnic differences in incidence. There is a slight predilection for women except among Chinese. Patients range from young to old. The parotid gland is primarily affected although a few tumors occur in the submandibular gland. Epstein Barr virus (EBV) infection of the malignant epithelial cells is demonstrable in most lymphoepithelial carcinomas, although less frequently in Caucasian patients. Most lymphoepithelial carcinomas arise de novo, a few occur in lymphoepithelial sialadenitis.

Discomfort, pain, or facial nerve palsy sometimes accompany swelling in the parotid or submandibular gland. Cervical lymphadenopathy is common. Tumors' durations have ranged from months up to 10 years.

At low-magnification, a lymphoid-dense stroma, often with germinal centers, is most conspicuous. At higher magnification, irregularly shaped aggregates of large epithelial cells within the lymphocyte-rich stroma become more readily evident. These epithelial cells are polygonal to slightly spindled cells with amphophilic to eosinophilic cytoplasm, large, round to oval, lightly basophilic to vesicular nuclei, and, often, one or more prominent nucleoli. They are variably arranged as small nests, cords, trabeculae, syncytial masses with indistinct cell borders, or isolated cells. Mitotic figures vary from few to numerous. The lymphoid-rich stroma is a mixture of lymphocytes and plasma cells that surround and permeate the carcinoma cells. The amount of collagenous stroma varies. Lymphoid markers confirm the benign nature of the lymphocytic infiltrate.

About 40% and 20% of tumors metastasize to cervical lymph nodes and distant sites, respectively, and both events indicate an adverse outcome.

The histopathologic, histochemical, immunohistochemical, ultrastructural, and molecular

features of nonkeratinizing, undifferentiated nasopharyngeal carcinoma of the so-called lymphoepithelioma type and lymphoepithelial carcinoma of the salivary gland are practically indistinguishable from one another.

BLEL AND LYMPHOMA

Despite recognition of the close association between salivary glands and lymphoid tissue, some investigator consider all salivary gland lymphomas as extranodal, whereas others distinguish between nodal and extranodal tumors. In one study, salivary gland lymphomas that arose within previously existing benign lymphoepithelial lesions were classified as extranodal, and the rest were classified as nodal in origin.[20]

Majority of lymphomas of major salivary gland arise de novo rather than from pre-existing salivary gland disease. Evolution from BLEL to lymphoma is thought to be a multistep process, with lymphoproliferation leading to non-Hodgkin's lymphoma, initation may be Sjogren's syndrome. High proportion of patient with Sjogren's syndrome demonstrates paraprotenimia and has correspondingly high frequency of non-Hodgkin's B-cell lymphoma.[21] Risk of lymphoma is believed to be more with primary Sjogren's syndrome. Lymphoma was more likely to develop in patients with parotid swelling than in those patients without swelling. Individuals with Sjogren's syndrome and BLEL have a lymphoproliferative disorder that increases chance of malignant transformation.[22] When lymphoma arises within a benign lymphoepithelial lesion, the process is generally slow and can take as long as 20 years. First stage is autoimmune exocrinopathy, second is pseudolymphoma and third stage is development of lymphoma.

CONCLUSION

Lymphoid tissue located in the head and neck region include multiple regional lymph node chains as well as mucosa associated lymphoid tissue of the conjunctiva, buccal and nasopharyngeal cavities (Waldeyer's ring), and thyroid and salivary glands. This region is a rich source of antigenic stimuli including infectious agents coming from the outside environment. Many reactive conditions that affect lymphoid tissue in this region may mimic neoplasia. In fact, distinguishing between benign and malignant lymphoid proliferations in the head and neck region is a relatively frequent diagnostic challenge and in many instances, this distinction is not straightforward. It therefore behooves the practicing pathologist to be able to recognize the benign lymphoproliferative disorders that affect this region so as to effectively guide the appropriate clinical management of such patients.

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